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Hyperthermic intraperitoneal chemotherapy with oxaliplatin and without adjuvant chemotherapy in stage IIIC ovarian cancer

N. Carrabin[1], F. Mithieux[1], P. Meeus[1], O. Trédan[2], J.-P. Guastalla[2], T. Bachelot[2], S.I. Labidi[2], I. Treilleux[3], M. Rivoire[1], I. Ray-Coquard[2]

[1]Centre Léon-Bérard, Department of Surgical Oncology, 28, rue Laennec, 69008 Lyon, France <nicolas.carrabin@yahoo.fr>

[2]Centre Léon-Bérard, Department of Medical Oncology

[3]Centre Léon-Bérard, Department of Cytopathology

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Abstract. **Objective.** To assess the feasibility and efficacy of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) without adjuvant chemotherapy for relapsed or persistent advanced ovarian cancer. **Methods.** This observational study included stage IIIC ovarian cancer patients due to undergo CRS (interval debulking or recurrent surgery) followed by HIPEC with oxaliplatin (460 mg/m^2) for 30 min. **Results.** Twenty-two patients (12 interval debulking procedures and 10 recurrence procedures) were enrolled between September 2003 and September 2007. HIPEC was not performed in four patients because of operative findings. No patient received adjuvant chemotherapy after HIPEC. Patients were followed up routinely until recurrence or death. Median peritoneal cancer index at surgery was 6 (range: 1-18). Before HIPEC, all patients had completeness of cytoreduction scores of 0 or 1. Median length of hospital stay was 21 days (range 13-65). Ten patients (55.6%) had CTCAE grade 3-4 toxicity, including three patients (16.7%) requiring reoperation. No postoperative mortality was observed. With a median follow-up of 38 months (CI 95% 23.8-39.2), median overall survival was not reached. The 3-year overall survival rate was 83% (CI 95% 54-95). Median disease-free survival was, respectively, 16.9 months (CI 95% 10.2-23.2) and 10 months (CI 95% 4.5-11.3) for patients undergoing interval debulking or recurrence surgery. **Conclusion.** HIPEC without adjuvant chemotherapy is both feasible and safe, but with a high rate of grade 3-5 toxicity. Survival results are encouraging but should be confirmed in a randomized trial. ▲

Key words: cytoreductive surgery, HIPEC, ovarian cancer, oxaliplatin

Introduction

Epithelial ovarian cancer is the second most common gynecologic malignancy in France [1] and in Europe. It is also the most lethal of all gynecologic malignancies, with a high mortality to incidence ratio [2]. Most patients present with advanced disease at the time of diagnosis, whereas dissemination of the cancer is often limited to the peritoneal cavity [3] for much of its natural history.

Complete surgical cytoreduction provides a substantial survival benefit for patients with locoregional disease, both at primary surgery [4-6] and, as reported more recently, at recurrence [7]. However, even after complete surgical cytoreduction, the majority of patients with advanced epithelial ovarian cancer ultimately experience tumor recurrence [8]. Many adjuvant treatments with intravenous cytotoxic agents have proved effective in ovarian cancer, particularly platinum compounds and taxanes [9].

On the basis of these observations, new aggressive procedures have been developed, and surgical efforts have been made to improve survival rates. Considering that intraperitoneally administered agents are associated with significantly increased drug exposure in the peritoneal cavity as compared to systemic agents [10], and that hyperthermia is both tumoricidal in itself [11] and likely to increase the cytotoxicity of platinum [12], it was proposed to combine hyperthermic intraperito-

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neal chemotherapy (HIPEC) and cytoreductive surgery (CRS) [13], as previously done for many other tumors spreading within the peritoneal cavity, such as colorectal or gastric tumors [14-16]. Ovarian carcinoma that develops slowly in the peritoneal cavity and involves only the peritoneum and adjacent intra-abdominal organs appeared ideally suited for locoregional therapy. Only few studies, with relatively small numbers of patients, have tested CRS and HIPEC in this disease [17-21], and they usually report the use of adjuvant chemotherapy after CRS + HIPEC.

To date, there is no scientific evidence to support the use of HIPEC as a standard therapy in ovarian cancer. The objectives of our study were to evaluate the feasibility and long-term results of HIPEC without adjuvant chemotherapy in stage IIIC ovarian cancer patients.

Materials and methods

This is an observational study designed in 2003 and is based on data from the medical records of consecutive patients with ovarian cancer.

Patient selection

Inclusion criteria were FIGO (International Federation of Gynecology and Obstetrics) stage IIIC ovarian cancer in relapse, FIGO stage IIIC ovarian cancer with suboptimal cytoreduction following primary surgery and platinum-taxane based chemotherapy (three to nine cycles) and with evidence of persistent peritoneal involvement, WHO performance status ≤ 2, age ≤ 70 years, and fully informed consent to undergo HIPEC.

Exclusion criteria were cancer histology other than serous or poorly differentiated carcinoma, evidence of nonresectable disease at preoperative evaluation, and anesthesiologic risk contraindicating HIPEC.

Preoperative evaluation

Preoperative assessment identified patients with potentially unresectable disease. Preoperative workup included clinical examination, thoracic, and abdominal CT scan and evaluation of serum Ca 125 level. Complete information about the procedure was given to the patients, and each decision of HIPEC was discussed and approved at a multidisciplinary consultation meeting.

Treatment plan and drug administration

Intravenous chemotherapy

HIPEC was performed in two clinical situations: ovarian cancer with nonoptimal cytoreduction at primary surgery (completion of initial treatment) and ovarian cancer in relapse.

All patients with nonoptimal cytoreduction at primary surgery received adjuvant intravenous chemotherapy after the first surgery, and CRS + HIPEC were performed next in case of evidence of persistent peritoneal involvement as a completion of initial treatment.

Patients with recurrence and with evidence of widespread disease on preoperative evaluation received intravenous chemotherapy before HIPEC to facilitate surgical resection. When preoperative evaluation indicated complete cytoreduction, no intravenous chemotherapy was given.

No patient received adjuvant chemotherapy after HIPEC.

Surgical procedure

Careful abdominal exploration was performed through a midline incision from xiphoid to pubis, under general anesthesia.

The goal of the surgical procedure was the removal of all macroscopically visible tumor nodules from the visceral or parietal peritoneum. After exploration of the abdominal cavity, the peritoneal cancer index (PCI) was calculated as described by Sugarbaker [22], and the feasibility of complete CRS was evaluated. When the procedure was considered unfeasible, the HIPEC option was rejected at that stage. When necessary, total or partial resection of an involved organ was performed. Intestinal anastomoses were performed before the HIPEC procedure.

Cytoreduction scoring

The completeness of cytoreduction (CC) was scored as proposed during the fifth international consensus meeting on peritoneal surface malignancies treatment [23], with CC0 corresponding to no residual disease, CC1 to residual nodules less than 2.5 mm in diameter, CC2 to residual nodules between 2.5 mm and 2.5 cm, and CC3 to residual nodules greater than 2.5 cm.

HIPEC procedure

HIPEC was performed as an open procedure at the end of surgery using the coliseum technique [22]. After suspension of the anterior abdominal wall using a Book-

walter retractor system (Aesculap inc., Le Locle, Switzerland), two inflow drains and three outflow drains were inserted into the abdominal cavity. Six temperature probes were placed in different parts of the abdomen (right and left subdiaphragmatic areas, mesenteric roots, Douglas pouch, inflow, and outflow drains) to allow good control of the temperature during HIPEC. The abdominal cavity was filled with a 5% glucose solution heated at 41-43 °C using a heat exchanger, two roller pumps, and a heater/cooler unit (Performer LRT, RanD S.r.l. Medolla, Italy).

HIPEC consisted of oxaliplatin (460 mg/m^2) for 30 min. The temperature recorded by each probe was monitored every 5 min during the procedure and an average of all measurements was calculated. Total operative duration, blood loss, and need for transfusion were recorded at the end of surgery.

Post-HIPEC management

All patients were admitted postoperatively to an intensive care unit for at least 24 h, and then transferred to the general surgery unit.

Toxicity and postoperative complications were evaluated using the CTCAE scale, version 3.0. [24]. All documented grade 3-5 side effects were recorded, and relation with CRS or HIPEC was reported when possible. Hematological toxicity was evaluated every 48 h during hospital stay by complete blood count and basic metabolic panel tests.

Hospital discharge, grade 3-5 complications, and reoperation were documented in the patients' medical records.

Follow-up, evaluation of response, and survival

Routine follow-up was performed every 4 months during the first 2 years, and then every 6 months thereafter. It included clinical examination, Ca 125 measurement, and a CT scan of the thorax and abdomen at every follow-up visit.

All patients undergoing ostomy surgery were reoperated for laparotomy closure within 6 months. A surgical exploration including systematic peritoneal biopsy was performed at that time.

Recurrence and progression were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) and Rustin's criteria. [25, 26] Recurrent carcinomatosis was diagnosed when patients presented clinical evidence of peritoneal carcinomatosis (ascites, digestive occlusion, and so on) or when peritoneal carcinomatosis was visible on a CT scan.

When recurrence was diagnosed, an adapted treatment was given as decided by the multidisciplinary consultation meeting (number of chemotherapy lines, radiotherapy, and iterative surgical resection). The time and type of recurrence, the nature of treatment, and date of death were recorded.

Median follow-up was calculated from the date of HIPEC to the date of last visit or date of death.

Statistical analysis

Survival rates and time to progression were analyzed by the Kaplan-Meier method using SAS® version 9.1. Overall survival (OS), disease-free survival (DFS) and carcinomatosis-free survival (CFS) were calculated from the date of HIPEC to, respectively, the date of death (OS), the date of relapse (DFS), and the date of carcinomatosis recurrence (CFS) or, in the absence of any event, to the date of last follow-up. Survival estimates were calculated using the Kaplan-Meier method [27]. Differences in survival estimates were assessed by the log-rank test [28]. Median follow-up was estimated by the reversed Kaplan-Meier method.

Results

Patient characteristics

Twenty-two patients were included between September 2003 and September 2007. The median age was 49 years (range 29-63). Patient characteristics are summarized in *table 1*.

HIPEC was performed for completion of initial treatment in 12 patients with stable disease after nonoptimal CRS followed by platinum-taxane based chemotherapy and for the treatment of recurrent disease in 10 patients (6 patients in first relapse, 2 in second relapse and 2 in third relapse). Nine patients with recurrent disease were platinum-sensitive (disease-free interval >6 months) and one was platinum-refractory (disease-free interval <6 months). All patients were previously treated with chemotherapy (1 to 3 lines).

Table 1. Patient characteristics.

Patient	Age (years)	Histology	HIPEC indication	Disease stage	PCI	HIPEC performed
1	49	SA	CIT	SD	7	yes
2	29	SA	CIT	SD	9	yes
3	49	SA	CIT	SD	3	yes
4	48	PDA	CIT	SD	3	yes
5	49	SA	CIT	SD	5	yes
6	48	SA	CIT	SD	1	yes
7	44	SA	CIT	SD	6	yes
8	53	SA	CIT	SD	13	yes
9	42	SA	CIT	SD	4	yes
10	52	SA	CIT	SD	9	yes
11	48	SA	First relapse	PS	14	yes
12	50	SA	Second relapse	PS	1	yes
13	46	PDA	First relapse	PS	6	yes
14	61	SA	First relapse	Platinum refractory	18	yes
15	49	SA	Third relapse	PS	9	yes
16	63	PDA	First relapse	PS	3	yes
17	63	SA	First relapse	PS	6	yes
18	42	SA	Third relapse	PS	4	yes
19	60	SA	First relapse	PS	15*	no
20	41	SA	CIT	SD	0**	no
21	48	SA	CIT	SD	19*	no
22	44	SA	Second relapse	PS	29*	no

PCI = peritoneal cancer index; PDA = poorly differentiated adenocarcinoma; SA = serous adenocarcinome; CIT = completion of initial treatment; SD = stable disease; PS = platinum sensitive.
* HIPEC not performed because complete cytoreduction was considered impossible.
** HIPEC not performed because no disease was evidenced (either macroscopic or microscopic) on multiple peritoneal biopsies.

HIPEC procedures

Four of the 22 patients (18%) did not receive HIPEC because of operative findings. HIPEC had then been planned for completion of initial treatment in two cases and for the treatment of recurrent disease in two cases. In three patients, lesions were considered not completely removable, and in one patient surgical exploration revealed no macroscopic or microscopic evidence of lesion.

Table 2 shows the characteristics of the HIPEC procedure in the 18 patients treated for completion of initial treatment or for recurrent disease: PCI, CC rate, proportion of patients undergoing organ resection and stoma, HIPEC temperature, length of surgery, estimated blood loss, and time to hospital discharge. Median PCI score was 6 (range 1-18). CC score after CRS was 0 or 1 for all patients. Respectively, 70% and 75% of the patients undergoing HIPEC for completion of initial treatment or for recurrent disease had bowel resection, and 30% and 75% required a stoma. The median total length of surgery was 395 min (range 145-600) and the median blood loss was 250 ml (range 50-1500). Five patients (28%) were transfused with red blood cells during the surgical procedure.

Toxicity

Ten patients (55.6%) had at least one grade 3-4 toxicity (3 of them had two), including 3 (16.7%) patients requiring reoperation. No death occurred in the first postoperative month. *Table 3* shows the different grade 3-4 complications observed. No grade 3-4 leucopoenia, no grade 3-4 glomerular filtration impairment or creatinine elevation was observed.

Survival

Median patient follow-up was 38 months (CI 95%, 23.8-39.2). Survival analysis did not include patients

Table 2. Characteristics in patients undergoing CRS + HIPEC for completion of initial treatment or for recurrent disease.

	PCI at surgical exploration	CC score	Bowels resection	Ostomy surgery	Splenectomy	HIPEC average temperature (°C)	Length of surgery (min)	Blood loss (ml)	Hospital discharge (days)
	Median (range)	*Number of patients (%)*				*Median [range]*			
Completion of initial treatment *n = 10*	5.5 (1-13)	CC0 = 8 CC1 = 2	7 (70%)	3 (30%)	4 (40%)	42 [41.7-44]	382 [180-480]	200 [50-700]	18 [13-29]
Recurrent disease *n = 8*	6 (1-18)	CC0 = 8 CC1 = 0	6 (75%)	6 (75%)	4 (50%)	42 [41.5-43]	480 [145-600]	450 [50-1500]	22.5 [13-65]
Total n = 18	6 (1-18)	CC0 = 16 CC1 = 2	13 (72%)	9 (50%)	8 (44%)	42 [41.5-44]	395 [145-600]	250 [50-1500]	21 [13-65]

PCI = peritoneal cancer index; CC = completeness of cytoreduction; CRS = cytoreductive surgery; HIPEC = Hyperthermic intraperitoneal chemotherapy.

Table 3. Complications observed (according to the CTCAE v3.0 classification [24]).

Category	Adverse event	Severity grade	Number of cases *n* (%)	Patient number
Blood/bone marrow	Low hemoglobin	3	2 (11)	11, 6
Gastrointestinal	Anastomotic leak (rectum)	3	1 (5)	16
	Fistula (pancreas)	4	1 (5)	14
Hemorrhage/bleeding	Hematoma (liver)	4	1 (5)	8
	Hematoma (retroperitoneal)	3	1 (5)	10
Infection	Sepsis with normal absolute neutrophil count	3	1 (5)	5
Metabolic/laboratory findings	Hyponatremia	3	1 (5)	1
Pulmonary/upper respiratory	Pleural effusion	3	3 (17)	14, 10, 18
	Pneumonitis	4	1 (5)	9
Vascular	Phlebitis	3	1 (5)	8

in whom HIPEC was not performed because of operative findings. Overall survival, DFS and CFS are shown in *figure 1*. The median OS was not reached, but OS rates at 2 and 3 years were, respectively, 92% (CI 95%, 67-99) and 83% (CI 95%, 54-95). The median CFS was 16.2 months (CI 95%, 9.3-22.7), and the median DFS was 11.3 months (CI 95%, 9.3-17.6). *Figure 2* shows the DFS curves of patients treated for completion of initial treatment or for recurrent disease, with median durations of 16.9 months (CI 95%, 10.2-23.2) and 10 months (CI 95%, 4.5-11.3). Patients receiving HIPEC for recurrent disease relapsed significantly earlier than patients receiving HIPEC for completion of initial treatment ($p = 0.03$).

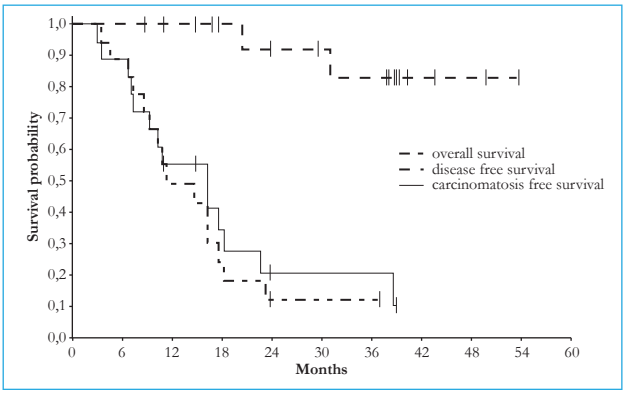

Figure 1. Overall survival, disease-free survival, and carcinomatosis-free survival after HIPEC.

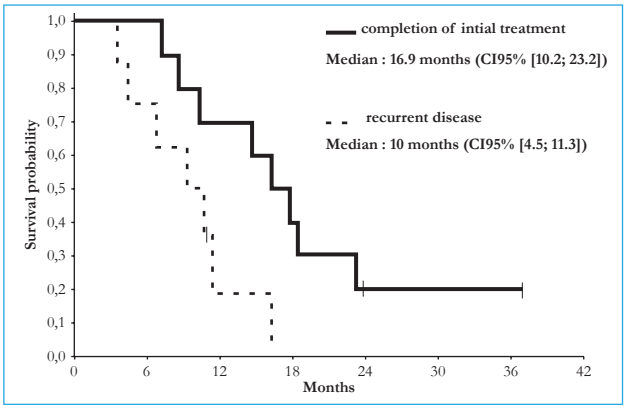

Figure 2. Disease-free survival in case of a procedure for completion of initial treatment or for recurrent disease.

Fifteen patients relapsed after HIPEC. Four patients developed distant metastases (abdominal skin $n = 2$ and distant lymph node $n = 2$), eight patients showed a locoregional relapse (carcinomatosis $n = 5$, locoregional lymph node $n = 1$, and carcinomatosis and locoregional lymph node $n = 2$), and three had both locoregional relapse and distant lymph node involvement.

All the patients who relapsed received chemotherapy, with a median of two lines (range 1-5). Two patients received radiotherapy, and six had iterative surgery.

Discussion

No randomized studies testing HIPEC in patients with ovarian cancer have been published to date because of poor patient accrual, and phase II studies often mix different disease stages, different HIPEC drugs, and different adjuvant strategies [29, 30]. Descriptive studies with strictly described patients, long follow-up, and precise outcome are needed. With a follow-up of 38 months, our study provides useful information about HIPEC in two clinical situations: completion of initial treatment after suboptimal surgery followed by chemotherapy and at the time of disease recurrence. The drug used for HIPEC was oxaliplatin. Single-agent oxaliplatin has demonstrated efficacy [31], associated with a favorable toxicity profile [10], in platinum-pretreated ovarian cancer patients.

Numerous phase I studies have reported on the feasibility of HIPEC in ovarian cancer [18, 32]. Our study confirms these earlier reports with no mortality but with an important 55.6% rate of grade 3-4 toxicities. In this study, we only recorded major toxic events (grade 3-5) and not minor toxicities. We used the CTCAE version 3.0 grading system to record toxicity in our patients, as it was the classification system adopted by an international panel of experts for assessing complications related to HIPEC and CRS [24]. Up to now, only few studies have used this classification system to assess toxicity [17, 18, 32, 33], and comparison between the different toxicity grading systems is difficult [32]. In addition, only few other studies have reported on the use of oxaliplatin for HIPEC in ovarian cancer. A prospective study by Fagotti *et al.* [33] using the same grading system has found 28% of major complications, which is much lower than the rate reported here. In their study, HIPEC was associated with no grade 3-4 metabolic complication, whereas we observed one patient with grade 3 hyponatremia, and grade 3-4 hemorrhagic complications occurred in two patients after treatment with an isotonic solution of oxaliplatin 460 mg/m^2. Elias *et al.* have reported a higher rate of hemorrhagic complications with hypotonic intraperitoneal oxaliplatin compared to the administration of an isotonic solution [34]. In our study, oxaliplatin 460 mg/m^2 was associated to a relatively high rate of grade 3-4 toxicities (55%) and is unreasonable to propose this treatment without scientific evidence of its clinical benefit. This is the reason why randomized phase III studies are urgently needed.

The cytoreduction preceding HIPEC is a time-consuming procedure, with a median duration of 395 min in our experience. For efficient operating theatre organization, treatment planning should be done carefully, based on clinical and radiological findings, to avoid wasting time on cancelled interventions. The objective of CRS should be a residual lesion size of 2.5 mm or less (CC0 or CC1 cytoreduction) prior to HIPEC, according to the expert consensus reached during the fifth international consensus meeting on peritoneal surface malignancies treatment [29]. Even though no consensus has yet been reached regarding the indication for HIPEC in case of suboptimal CRS [35], we chose not to use it in patients with suboptimal cytoreduction. We based our decision on evidences that the diffusion of intraperitoneally administered drugs into peritoneal tumors reaches a maximum of 2.5-5 mm, even when treatment is associated with hyperthermia [36-38], and that the benefits of HIPEC after suboptimal cytoreduction are limited in terms of outcome [17, 18,

39-41]. However, both peritoneal carcinomatosis and CC remain difficult to ascertain preoperatively, even with modern imaging techniques [42, 43]. In our study, minimal preoperative assessment with a CT scan, serum CA 125 measurement, and complete physical examination failed to predict operative findings in 4 of the 22 patients (18%). Other authors advise systematic laparoscopic evaluation of peritoneal carcinomatosis before planning surgery for HIPEC to avoid unnecessary laparotomy [44]. We now perform systematic FDG-Pet/CT (Fluorodeoxyglucose-Positron emission tomography with computed tomography) imaging for the preoperative staging.

With a median follow-up of 38 months, the median OS was not reached in our study. The 3-year OS rate was 83%. A literature analysis shows similar values with median OS durations ranging from 24 months to 64 months [18-20] and 2-year survival rates between 55% and 60% [17, 45]. However, due to the large heterogeneity of the populations studied, comparison with our results is difficult.

In our study, the median DFS of patients undergoing HIPEC for recurrent disease was 10 months. Other studies using HIPEC at time of recurrence have reported post-HIPEC DFS durations between 10 and 40 months [17, 18, 21, 33, 39]. In patients undergoing HIPEC for completion of initial treatment (evidence of persistent disease after first suboptimal surgery followed by chemotherapy), the median DFS was 16.9 months in our study versus 40.6 months in the study reported by Ryu *et al.* of HIPEC for second look or interval debulking in patients with residual disease less than 1 cm [19]. However, it is not known how many patients were in each group. Indeed, survival is expected to be different whether HIPEC is performed at the time of second look surgery for consolidation after complete prior cytoreduction and adjuvant chemotherapy or used for interval surgery after sub-optimal prior surgery and chemotherapy.

As shown in *table 4*, most authors are inclined to give adjuvant chemotherapy after HIPEC, even if its tolerance is not known. Fagotti *et al.* [33], who have used oxaliplatin HIPEC in association with adjuvant chemotherapy in a population similar to our patient population (recurrent disease surgery in platinum-sensitive patients), have found a median DFS of 10 months. We did not use adjuvant chemotherapy after HIPEC, but we also observed a median DFS of 10 months in patients with recurrent disease. No scientific evidence supports the benefit of systemic chemotherapy after HIPEC. Furthermore, the effects of systemic chemotherapy may interfere with those of HIPEC after complete cytoreduction, and the survival reported in phase II studies may be associated to either HIPEC or adjuvant chemotherapy.

In a recent meta analysis, Bristow *et al.* [7] have identified only two parameters associated with OS improvement in patients with recurrent ovarian cancer: year of treatment and complete CRS at the time of recurrence. Up to now, no compelling evidence has emerged about the use of HIPEC in ovarian cancer due to the lack of phase III trials, but results of observational and retrospective comparative studies are encouraging. As in our study, HIPEC is always associated with a maximal surgical effort toward complete cytoreduction, thus making it difficult to differentiate between the effects of peritoneal chemotherapy and those of CRS. The apparent survival benefit reported in observational studies of HIPEC could also be due to the maximal cytoreductive effort made before the intraperitoneal hyperthermic administration of the cytotoxic agent. Furthermore, the intraperitoneal hyperthermic administration of cytotoxic agents after CRS is associated with increased toxicity as compared with maximal CRS alone [32, 46]. In addition, numerous targeted cancer therapies based on the new understanding of molecular pathways within normal and malignant cells are currently in clinical trial [47]; these therapies might well modify the place of HIPEC in the treatment of ovarian cancer. All these observations suggest the need for randomized phase III trials of CRS with and without HIPEC in ovarian cancer.

In conclusion, HIPEC is feasible but is associated with a high rate of grade 3-5 complications and should therefore be administered by trained clinicians. The treatment is associated with a DFS of 11 months, but median OS is still not reached in selected cases after a 38-month median follow-up. The outcome of stage III ovarian cancer remains poor, but the combination of CRS and HIPEC could be an interesting therapeutic option. No consensus has yet been reached about indication, drugs, and doses for HIPEC. Randomized phase III studies are needed to determine the exact therapeutic value of the combination of CRS and HIPEC compared to CRS alone and the therapeutic value of adjuvant chemotherapy after HIPEC. ▼

Table 4. Results of other studies.

Authors year [Ref]	Patient *n*	Cancer stage: *n*	Disease status: *n*	Agent	Cytoreduction: *n* (%)	Adjuvant chemotherapy	Median DFS in months	Median OS in months	Five years OS rate
Ryu, 2004 [19]	57	Ic-II: 22 III: 35	Second LS/IDS	Carboplatin Interferon α	R0-R1: 48 (84%) R2: 9 (16%)	NR	Stage III: 26 III + R0-R1: 40	NR	Stage III: 53%
Piso 2004 [40]	19	III: 14 IV: 5	PS: 9 RDS: 11	Cisplatin mitoxantron	R0: 9 (47%) R1-R2:10 (53%)	Yes - *n* = 9 No - *n* = 10	NR	R0: 28 R1-R2: 20	15%
Zanon 2004 [45]	30	III-IV	PS: 8 RDS: 22	Cisplatin	CC0-CC1: 23 CC2: 7	NR	CC0-CC1: 24 CC2: 4	CC0-CC1: 37 CC2: 11	NR
Gori 2005 [30]	29	IIIB-IIIC	Second LS	Cisplatin	CC0	NR	57	64	NR
Reichmann 2005 [41]	13	III-IV	PS: 9 RDS: 4	Cisplatin	CC0-CC1: 11 CC2:2	NR	15	NR	NR
Rufian, 2006 [20]	33	III: 33	PS: 19 RDS: 14	Paclitaxel	R0: 17 (52%) R1: 11 (33%) R2: 5 (15%)	Yes	PS: 25 RDS: 31	PS: 38 RDS: 57	NR
Raspagliesi 2006 [21]	40	III-IV	Second LS: 13 RDS: 27	Cisplatin Mitomycin Doxorubicin	CC0: 33 CC1: 7	NR	Mean: 24	26	15%
Helm 2007 [18]	18	I: 2 III: 13 IV: 3	RDS: 18	Cisplatinum Mitomycin C	CC0: 11 (61%) CC1: 4 (22%) CC2:3 (17%)	Yes - *n* = 12 No - *n* = 6	10	31	NR
Cotte 2007 [17]	81	I-II: 7 III: 71 IV: 3	RDS: 77 IDS: 4	Cisplatin	CCR0: 45 (55%) CCR1: 20 (25%) CCR2: 16 (20%)	Yes - *n* = 43 No - *n* = 38	CCR0: 27 CCR1:NR CCR2:NR	CCR0: 55 CCR1:17 CCR2: 5	NR
Di Giorgio 2008 [39]	47	III-IV	PS: 22 RDS: 18 IDS: 4 Second LS: 3	Cisplatin	CC0: 30 (64%) CC1: 12 (25%) CC2: 5 (11%)	Yes - *n* = 45 No - *n* = 2	CC0: 24 CC1: 13 CC2: 6	CC0: 26 CC1: 13 CC2: 12	17%
Fagotti 2009 [33]	25	II: 2 III:21 IV:2	RDS	Oxaliplatin	CC0: 23 CC1: 2	Yes	10	NR	NR
Present study	18	IIIc	IDS: 10 RDS: 8	Oxaliplatin	CC0: 16 CC1: 2	No	IDS: 17 RDS: 10	>38	NR

DFS = disease-free survival; OS = overall survival; CC0 = no residual disease, CC1 = residual disease <2.5 mm, CC2 = residual disease >2.5 mm; R0 = no residual disease, R1 = residual disease <1 cm, R2 = residual disease >1 cm; CCR0 = no residual disease, CCR1 = residual disease <5 mm, CCR2 = residual disease >5 mm; PS=primary surgery; RDS=recurrent disease surgery; IDS=interval debulking surgery; second LS: Second-look surgery; NR: not reported.

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Conflict of interest. None.

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